Objectives: In the mid-90s, the first mathematical models addressing healthcare-associated infections (HCAI) were introduced. Since then, these models have contributed to an increased understanding of hospital epidemiology. We conducted a systematic review in order to establish 1) how mathematical models have been applied in the field of HCAI, 2) how the methods and model structures have developed over time and 3) what the results of these models have shown. This was done in order to synthesise key lessons learnt from these models and provide directions for future research in the area of modelling HCAI. Methods: We searched MEDLINE, EMBASE, CINAHL plus and the grey literature using search terms for mathematical modelling, HCAI and relevant organisms. Results: The first mathematical models of HCAI aimed at conceptualising transmission dynamics in single wards using deterministic approaches. Following this, stochastic models began to include chance due to its importance to the transmission process (particularly in small patient populations). The dominant pathogen studied is methicillin resistant Staphylococcus aureus. Others include vancomycin resistant enterococci and Clostridium difficile. Models have explored a multitude of factors important to HCAI transmission and control, for example, antibiotic effects and the development of resistance, variability in transmission routes, effectiveness of interventions and differences in transmission between strains or settings (including community transmission). Higher awareness of the significance of HCAI has lead to improved national and international surveillance systems, leading in turn to greater availability of data to inform modelling studies. This has been coupled with the development of more sophisticated methods e.g. for model parameterisation (e.g. Markov Chain Monte Carlo methods) and characterising uncertainty, and has led to improved model validation. Conclusion: The ecology and epidemiology of HCAI can be complex. Mathematical models have proved to be useful tools to aid our understanding of the spread of these infections and the likely impact of control measures. Improved national and international data collection initiatives have enabled development of more realistic models, however new insights and questions facing the field call for further elaboration and collaboration.